Biol 398/Math 388 Assignment #5:

A simple chemostat model of nutrients and population growth

Background. The chemostat is an idealization of a reactor for growing populations of cells like yeast. Nutrients are fed continuously at a fixed flow rate and concentration, and effluent is extracted at a fixed flow rate. A slight subtlety in the extraction part is that what is extracted is at a fixed flow rate, to keep the volume constant, but the effluent has a concentration that depends on the reaction. An illustration of the chemostat is given below.

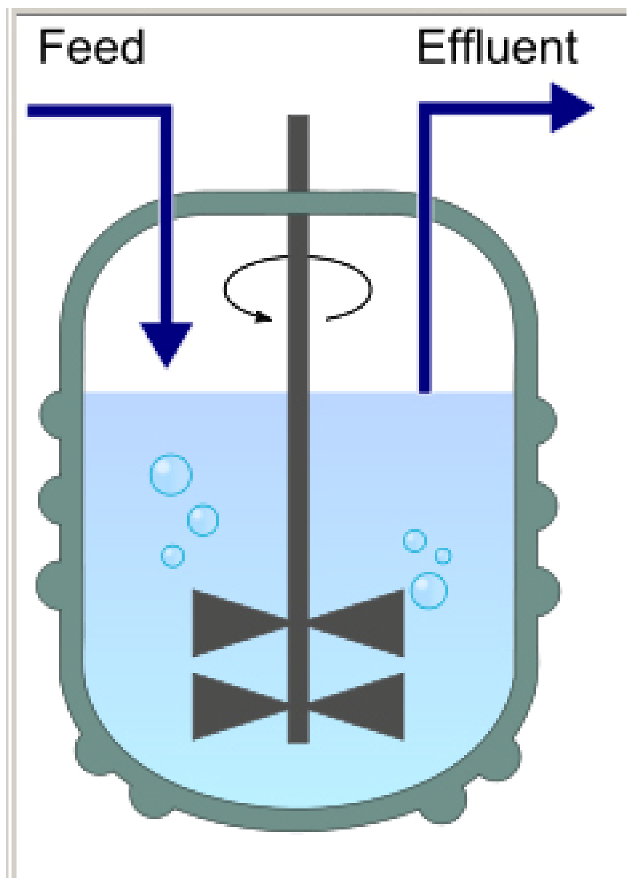

Figure 1. Chemostat cartoon from Wikipedia.

The basic assumption of the chemostat is that the contents are sufficiently well mixed that the concentration of the mixture is uniform throughout the container. Under this assumption, we do not need to consider spatial effects or non-uniformity of nutrients and cells: all cells have equal access to nutrient.

If the dilution rate is D in units of (1/time), and the feed concentration is u (in concentration units, mass or molar), and the volume of the mixture is V (and that's constant: the effluent outflow rate is assumed

the same as the inflow dilution rate), then the concentration of the nutrient $n(t)$ can be determined as follows:

Rate of change of nutrient = inflow rate – outflow rate – rate consumed in the tank.

Now, the inflow rate is $D*u$ (and this is assumed to be a constant, independent of time). The outflow rate is $D*n(t)$, because the effluent is extracted from the uniform, well-mixed tank contents. Thus, we have

$$\frac{dn}{dt} = Du - Dn(t) - \text{consumption rate}$$

For the moment, if we assume no consumption, one can apply Math 245 or Math 123 methods to find a formula for $n(t)$, assuming $n(t=0) = n_0$ is the initial concentration of nutrient in the tank at the start.

$$\begin{aligned}
&\frac{dn}{dt} = Du - Dn(t) \\
&\frac{1}{u-n}\frac{dn}{dt} = D \\
&-\ln(u-n) + \ln(u-n_0) = Dt \\
&n(t) = u - (u-n_0)e^{-Dt}
\end{aligned}$$

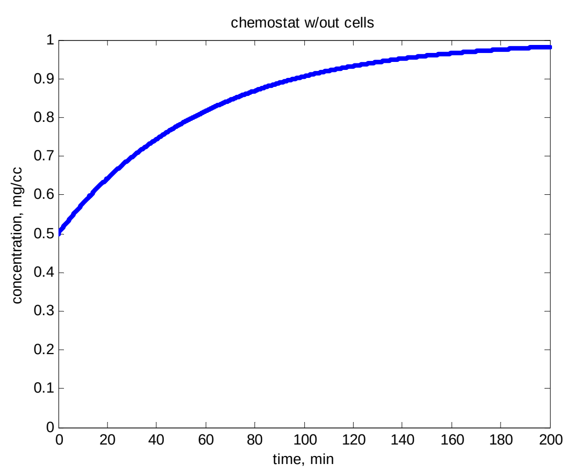

Figure 2. Chemostat equilibrating with only nutrient influx.

To introduce cells, we can take a number of modeling approaches. First, we can assume that the cell population is in stationary phase, meaning the size of the cell colony is constant in time. Using our simple Michaelis Menten model (which is also called the Monod model in the context of cell population growth) for the uptake of nutrients, we might consider

$$\frac{dn}{dt} = Du - Dn(t) - yV_{\max}\frac{n}{K+n}$$

to capture inflow, outflow, and metabolism of the nutrient. The "new" parameter is y, the concentration of yeast cells in the mixture.

Population dynamics. As one might imagine, the yeast cell population is not a constant. Rather, the population may grow and decline. The modeling of this process can be challenging, and while there are many "standard" models, there is no complete agreement on which one is "right" or even "best." The three most common are the Malthus model (or linear birth-death model), the logisitic model, and the Gompertz model. Each of these model the population as having a net rate of change roughly corresponding to "births" and "deaths."

The Malthus model is the most straightforward. The rate of change of the population is a sort of outflow/inflow balance: rate of change = birth rate – death rate. Each of these rates is a linear function of the population size y(t). The birth rate is b*y(t) and the death rate is d*y(t). The idea is that some fraction of the population reproduce in a time period, and some fraction of the population die in a time period. Thus

$$\frac{dy}{dt} = by - dy = ry,$$

Where r is the net growth rate. The solution of this differential equation is $y(t) = y_0 e^{rt}$ which either remains constant if r=0, grows exponentially (without bound) if r>0, or decays toward 0 if r<0.

To tweak this model to include nutrients, one could simply modify the growth rate to capture the consumption of nutrients:

$$\frac{dy}{dt} = yrV_{\max} \frac{n}{K+n},$$

So that the net growth rate depends on the nutrient level. This model leads to a coupled pair of differential equations, because the consumption model depends on the size of the population:

$$\begin{aligned} \frac{dn}{dt} &= Du - Dn(t) - yV_{\max} \frac{n}{K+n} \\ \frac{dy}{dt} &= yrV_{\max} \frac{n}{K+n} \end{aligned}$$

How does this system behave? More on this matter later.

The logistic model of population growth assumes that the net growth rate of the population depends on the population size:

$$\frac{dy}{dt} = r\left(1 - \frac{y}{M}\right)y,$$

So that the net growth rate is $r*(1\text{-}y/M)$, a function that is nearly = *r* when the population size is small, and decreases (linearly) toward 0 as *y* gets close to *M*. The parameter *M* is often called the carrying capacity, and this term conveys the idea that the environment somehow restricts the size to which the population can grow. One can show (using math 245/123 methods) that the population will tend toward *M* as *t* increases, no matter what the initial population size is (as long as it's positive to start). How do we modify this model to include nutrients? Either through *r* (as we did with Malthus) or through *M* thinking that the nutrient availability would impact the carrying capacity or limiting population size) or both!

The assignment.

(1) Consider the nutrient/cell population model

$$\frac{dn}{dt} = Du - Dn(t) - yV_{\max}\frac{n}{K+n}$$
$$\frac{dy}{dt} = yrV_{\max}\frac{n}{K+n}$$

- First, make sure you understand which variables are the state variables (dependent variables that determine the concentrations) and which variables are parameters (e.g., rate constants).
- Simulate this system with different values for the constants and the initial concentrations of nutrients and cells. The initial nutrient level can be =0, but the constants and the initial cell population size need to be positive. Can you make any observations about how the system behaves? The matlab models of the enzyme kinetics may be helpful: this system has two state variables, so you'll need x(1) and x(2), dxdt(1) and dxdt(2) as in the Michaelis-Menten substrate/product model.

(2) Adapt the system to a logistic growth model. We'll start with a nutrient dependent carrying capacity, *M=a*n*. The carrying capacity increases linearly with the nutrient level.

$$\frac{dn}{dt} = Du - Dn(t) - yV_{\max}\frac{n}{K+n}$$
$$\frac{dy}{dt} = yr\left(1-\frac{y}{an}\right)$$

- Simulate this system with different values for the constants and the initial concentrations of nutrients and cells. The initial nutrient level can be =0, but the constants and the initial cell population size need to be positive. Can you make any observations about how the system behaves?
- Suggest some additional adjustments. For example, look at the nutrient dependent growth rate in the Malthus model. Or, think about the waste products the yeast might produce. Are any of them toxic to the yeast? Where might that lead?